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Published in:
International Journal of Radiation Oncology Biology Physics

DOI:
10.1016/j.ijrobp.2012.01.050

Publication date:
2012

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation: Breast Cancer

Simultaneous Integrated Boost Irradiation After Breast-Conserving Surgery: Physician-Rated Toxicity and Cosmetic Outcome at 30 Months' Follow-Up

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Received Jun 13, 2011, and in revised form Jan 14, 2012. Accepted for publication Jan 16, 2012

Summary

Three-dimensional conformal radiotherapy with a hypofractionated, simultaneous integrated boost (3D-CRT-SIB) can be used as part of breast-conserving therapy. In this prospective study of 940 patients treated with 3D-CRT-SIB, cosmetic outcome (CO) and toxicity were assessed until 5 years after radiotherapy. Toxicity and CO were not impaired after 3D-CRT-SIB. Furthermore, fibrosis was not significantly associated with radiotherapy parameters.

Purpose: To evaluate toxicity and cosmetic outcome (CO) in breast cancer survivors treated with three-dimensional conformal radiotherapy with a hypofractionated, simultaneous integrated boost (3D-CRT-SIB) and to identify risk factors for toxicity, with special focus on the impact of age.

Methods and Materials: Included were 940 consecutive disease-free patients treated for breast cancer (Stage 0–III) with 3D-CRT-SIB, after breast-conserving surgery, from 2005 to 2010. Physician-rated toxicity (Common Terminology Criteria for Adverse Events version 3.0) and CO were prospectively assessed during yearly follow-up, up to 5 years after radiotherapy. Multivariate logistic regression analyses using a bootstrapping method were performed.

Results: At 3 years, toxicity scores of 436 patients were available. Grade ≥2 fibrosis in the boost area was observed in 8.5%, non-boost fibrosis in 49.4%, pain to the chest wall in 6.7%, and fair/poor CO in 39.7% of cases. Radiotherapy before chemotherapy was significantly associated with grade ≥2 boost fibrosis at 3 years (odds ratio [OR] 2.8, 95% confidence interval [CI] 1.3–6.0). Non-boost fibrosis was associated with re-resection (OR 2.2, 95% CI 1.2–4.0) and larger tumors (OR 1.1, 95% CI 1.0–1.1). At 1 year, chest wall pain was significantly associated with high boost dosage (OR 2.1, 95% CI 1.2–3.7) and younger age (OR 0.4, 95% CI 0.2–0.7). A fair/poor CO was observed more often after re-resection (OR 4.5, 95% CI 2.4–8.5), after regional radiotherapy (OR 2.9, 95% CI 1.2–7.1), and in larger tumors (OR 1.1, 95% CI 1.0–1.1).

Conclusions: Toxicity and CO are not impaired after 3D-CRT-SIB. Fibrosis was not significantly associated with radiotherapy parameters. Independent risk factors for fibrosis were chemotherapy after radiotherapy, re-resection, and larger tumor size. Re-resection was most predictive for worse CO. Age had an impact on chest wall pain occurrence.

Keywords: Toxicity, Cosmetic outcome, Breast cancer, Radiotherapy

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Presented in oral form at the 29th Annual Meeting of the European Society for Therapeutic Radiology and Oncology (ESTRO), in Barcelona, Spain, on September 12–16, 2010.

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 83, No. 4, pp. e471–e477, 2012
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doi:10.1016/j.ijrobp.2012.01.050

Introduction

Breast-conserving therapy (BCT), consisting of breast-conserving surgery followed by radiotherapy (RT), is considered the standard of care for early-stage breast cancer (1). In BCT, whole-breast irradiation with the addition of a boost to the tumor bed reduces the risk of local recurrence in invasive breast cancer (2).

Since 2005, in our department, patients undergoing breast-conserving surgery are irradiated with three-dimensional conformal RT with a simultaneous integrated photon boost (3D-CRT-SIB), as previously described (3). Compared with sequential boost techniques, 3D-CRT-SIB provides increased dose homogeneity, with less unintended excessive dose outside the boost area, in combination with a higher dose per fraction to the tumor bed, resulting in a shorter overall treatment time. Acute toxicity is relatively mild (3). With the 3D-CRT-SIB technique, the daily fraction to the boost area is 2.3 or 2.4 Gy. Because of the higher dose per fraction, there might be an increased risk of fibrosis and subsequent impaired cosmetic outcome (CO). The first results on clinical outcome are excellent, with a 3-year local control rate of 99.6% (4). Yet there are no data on toxicity and CO after this hypofractionated 3D-CRT-SIB technique.

The primary aim of the present study was to evaluate physician-rated toxicity and CO in a series of early-stage breast cancer patients treated with 3D-CRT-SIB at a median of 30 months of follow-up. In addition, we tried to identify prognostic factors for toxicity and CO, with special focus on the impact of age on the risk of developing toxicity.

Methods and Materials

Study population

This prospective cohort included 940 consecutive disease-free women treated with RT for invasive breast cancer (Stage I–III) or ductal carcinoma *in situ* (DCIS), after breast-conserving surgery. All patients were irradiated at the Department of Radiation Oncology of the University Medical Center Groningen from January 1, 2005 to June 1, 2010. During the study period, 3D-CRT-SIB was the standard technique for postlumpectomy RT in all invasive carcinoma and in patients with pure DCIS with an indication for boost irradiation. Patients with a previous malignancy, patients previously irradiated to the chest wall, and patients treated with neoadjuvant chemotherapy were excluded.

The mean (SD) age was 58.7 (10.2) years at start of RT. The majority of patients, 84.6%, had invasive breast cancer, of which 71.5% ($n = 672$) had tumors $\leq$2 cm in diameter. Mean tumor diameter was 16 (7.5) mm. Patient, tumor, and treatment-related characteristics are summarized in Table 1.

Since April 2008, we subjected all new patients and all patients previously treated in yearly follow-up to a standard follow-up program, in which toxicity, quality of life, and tumor status were prospectively scored and collected according to the hospital institutional review board regulations. Median follow-up was 30 months (range, 6–54 months), with last follow-up set on December 31, 2010.

Table 1 Patient characteristics ($n = 940$)

Characteristic	*n*	%
Age at start of RT (y)		
≤50	214	22.8
>50	726	77.2
Location		
Lateral	496	52.8
Medial	186	19.8
Rest	204	21.7
Missing	54	5.7
Pathological T stage		
pT *in situ*	35	3.7
pT1	672	71.5
pT ≥2	233	24.8
Pathologic N stage		
pN0	655	69.7
pN+	255	27.1
pNx	30	3.2
Re-resection		
No	831	88.4
Yes	109	11.6
Axillary clearance		
No	656	69.8
Yes	284	30.2
Adjuvant chemotherapy		
No	602	64.0
Yes	338	36.0
Adjuvant hormonal therapy		
No	551	58.6
Yes	389	41.4
Adjuvant trastuzumab		
No	901	95.9
Yes	39	4.1
Regional RT		
No	880	93.6
Yes	60	6.4
Treatment sequence		
Surgery-RT	602	64.0
RT-chemotherapy	155	16.5
Chemotherapy-RT	183	19.5
Boost tumor bed		
Low (64.4 Gy)	705	75.0
High (67.2 Gy)	235	25.0
Smoking		
No	770	81.9
Yes	170	18.1

Abbreviation: RT = radiotherapy.

Surgery

Primary surgery was performed in nine hospitals in the northern part of The Netherlands. All patients were treated with lumpectomy. In case of more than focally involved resection margins, re-resection was performed ($n = 109$; 11.6%) to achieve clear surgical margins. Axillary staging was done with sentinel node biopsy (SN) in invasive carcinoma. Axillary clearance, which followed positive results on SN or positive cytology in the clinically node-positive axilla, was performed in 283 patients (30.1%). In selected cases of pure DCIS, an SN was carried out as well.

Radiotherapy

Radiotherapy was delivered with hypofractionated 3D-CRT-SIB, as previously described by van der Laan *et al.* (3). Computed

tomography-planned breast irradiation with whole-breast irradiation and a boost dose to the tumor bed area were given simultaneously. Two opposing tangential beams were directed to the whole breast. In general, the boost plan consisted of three equally weighted photon beams. The fractionation schemes used were 28 × 1.8 Gy to the whole breast and a boost of 2.3 Gy (75.0%) or 2.4 Gy, resulting in a total dose of 64.4 or 67.2 Gy. The highest dose was administered in case of focally positive resection margins. These fractionation schedules are biologically equivalent to 25 × 2 Gy with a sequential boost dose of 8 × 2 or 10 × 2 Gy using an α/β of 10 for tumor control.

Regional RT ($n = 60$; 6.4%), including irradiation of the axillary, supra-, and infraclavicular nodal areas (and including the internal mammary nodes in 7 cases), was applied in case of more than three positive axillary lymph nodes or a positive apical lymph node.

Systemic therapy

Adjuvant systemic therapy was indicated in patients with node-positive disease and high-risk node-negative tumors. Patients were classified as high risk depending on tumor size, grade, hormonal receptor status, and age. In total, 338 women were treated with chemotherapy, of whom 80.5% received 5-fluorouracil, epirubicine, and cyclophosphamide (FEC). In 16.3% of the patients, FEC was combined with taxane chemotherapy. In most patients with node-positive disease, RT was given after completion of chemotherapy, whereas in high-risk node-negative patients, RT was given before chemotherapy. Hormonal therapy, tamoxifen, or aromatase inhibitors, depending on menopausal status, were indicated for all hormonal receptor-positive disease in the node-positive and high-risk node-negative group. In patients receiving chemotherapy, trastuzumab was indicated in tumors overexpressing human epidermal growth factor receptor 2.

Toxicity assessment

After completion of RT, patients underwent routine yearly follow-up to 5 years after RT. As of April 1, 2008, all patients were subjected to the standard follow-up program. During follow-up, physician-rated toxicity, according to Common Terminology Criteria for Adverse Events version 3.0 (5), and CO were assessed. Cosmetic outcome was scored according to a commonly used 4-point scale, ranging from excellent to poor global cosmetic result, comparing the treated with the untreated breast (6).

At 12, 24, 36, and 48 months, toxicity scores of 562, 515, 436, and 200 patients were available, respectively, which corresponds with an excellent compliance of >98% at all time points. Selected endpoints were grade ≥2 fibrosis in the boost area, any-grade fibrosis in the non-boost area, grade ≥2 telangiectasia, any-grade breast edema, any-grade pain to the chest wall, any-grade rib fracture, and fair/poor CO.

Statistical analysis

Follow-up time was calculated as the interval between date of completion of RT and last follow-up visit. Prevalence of toxicities and corresponding 95% confidence intervals were presented at different time points: 12 (≥6, <18), 24 (≥18, <30), 36 (≥30, <42), and 48 (≥42, <54) months.

Multivariate logistic regression analyses, with forward selection and extended bootstrapping technique as described by Beetz *et al.* (7), were performed to study the influence of clinicopathologic factors on toxicity and CO. Fibrosis in the boost area, fibrosis in the non-boost area, telangiectasia, and CO were evaluated at 36 months of follow-up. Evaluation of breast edema and pain to the chest was chosen at 12 months because of an observed decrease over time. Because of the low number of observed rib fractures, no analysis was performed for this endpoint. The following covariates were considered: age at start of RT (≤50/>50 years); re-resection (no/yes); tumor location (lateral/medial/other); pathologic tumor size (continuous in millimeters); axillary clearance (no/yes); chemotherapy combined with sequence of treatment (surgery-RT/chemotherapy-RT/RT-chemotherapy); hormonal therapy (no/yes); trastuzumab (no/yes); regional RT (no/yes); boost dose tumor bed (low/high); and smoking (no/yes, defined as smoking during RT).

The analyses for model building were performed in MATLAB (version R2009b; MathWorks, Natick, MA) and were repeated in SPSS version 16.0 (SPSS, Chicago, IL) to calculate odds ratios. A p value ≤0.05 was considered statistically significant.

Results

Toxicity outcomes

Grading of toxicities is presented in Fig, with number of events listed in Table 2. Comparing the prevalence of events at every time point, grade ≥2 fibrosis in the boost area seemed stable over time. Prevalence of grade ≥2 fibrosis to the boost area ranged from 10.4% at 12 months to 6.6% at 48 months of follow-up. This stability over time could also be observed in fibrosis outside the boost area. At 36 months, the prevalence of any-grade fibrosis in the non-boost area was highest (49.5%). Telangiectasia was observed infrequently, with grade ≥2 telangiectasia of 3.7% at 36 months. Both breast edema and mild or worse pain to the chest wall gradually decreased over time, with a decrease in breast edema from 26.2% at 12 months after completion of RT to 6.1% at 48 months. Pain of the chest wall decreased from 12.2% to 7.5%. Overall, seven rib fractures (0.7%) were reported. Physician-rated CO seemed fairly stable over time. At 48 months, 64.1% of patients had a good or excellent CO.

Multivariate regression analyses

Results of the multivariate regression analysis are shown in Table 3. Sequencing chemotherapy after RT was the only significant factor associated with grade ≥2 fibrosis in the boost area, compared with no chemotherapy at 36 months of follow-up. Comparing chemotherapy before or after RT, an increased risk of grade ≥2 fibrosis in the boost area in patients who received chemotherapy after RT was observed (odds ratio 4.9, 95% confidence interval 1.5−16.1, $p = 0.008$). The presence of fibrosis in the non-boost area at 3 years was significantly associated with both larger tumor size and the performance of a re-resection. No significant risk factors could be identified for grade ≥2 telangiectasia. Breast edema at 12 months was seen more frequently after axillary clearance and in patients with larger tumors. Pain to the chest wall was the only endpoint to which age was associated. At 12 months, a significant 2.4-fold higher risk of pain to the chest wall was observed in younger patients (≤50 years) and a 2.1-fold

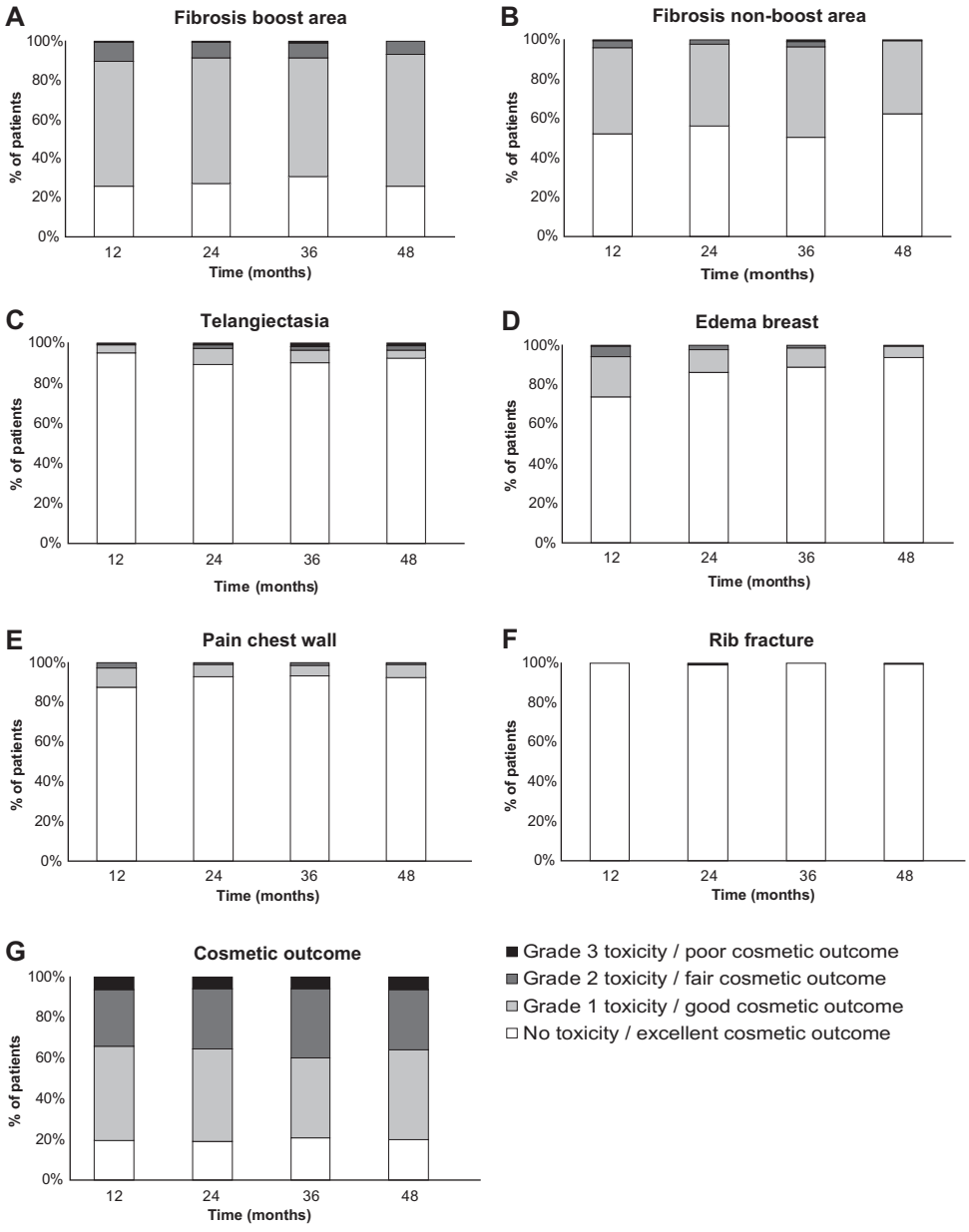

Fig. Cross-sectional physician-rated toxicity: (A) fibrosis boost area, (B) fibrosis non-boost area, (C) telangiectasia, (D) edema breast, (E) pain chest wall, (F) rib fracture, and (G) cosmetic outcome, described in proportions of patients at different time points (12, 24, 36, and 48 months after radiotherapy) in women treated with three-dimensional conformal radiotherapy with a hypofractionated, simultaneous integrated boost after breast-conserving surgery.

increase in patients who received a boost of 67.2 Gy. After re-resection the risk of a fair or poor CO was increased by four-fold. Furthermore, larger tumors and regional RT were significant prognostic factors for worse CO.

Discussion

In this article we present the first results on toxicity in breast cancer patients treated with the 3D-CRT-SIB technique. In general, physician-rated toxicity was not impaired and was comparable to the known literature, with a prevalence of grade $\geq$2 fibrosis in the boost area of 8.5% at 3 years after RT. Patients treated with a high boost dosage were more at risk of developing pain to the chest wall.

For fibrosis, similar results have been previously reported, with grade $\geq$2 fibrosis in the boost area or the operation site ranging from 7.2% to 26.8%. These patients were treated with breast-conserving surgery combined with whole-breast irradiation with or without a boost (8, 9). Although in the higher range, the rated fibrosis in the whole breast in our series, defined as the area outside the boost, corresponds with publications of others, ranging from 32.7% to 48.2% (8–11).

When using 3D-CRT-SIB, a higher dose per fraction is delivered to the boost area, which may result in an increased risk of fibrosis in this area. On the other hand, less excessive dose is delivered outside the boost area (3), possibly resulting in less fibrosis in the remaining breast. Furthermore, with the current knowledge on the α/β for tumor control of 4.6 (12), the chosen hypofractionated regimen in

Table 2 Number of events at different times of follow-up

	Time since completion of radiotherapy (no. of toxicity scores available)											
	12 mo (562)			24 mo (515)			36 mo (436)			48 mo (200)		
Endpoint	*n*	%	95% CI	*n*	%	95% CI	*n*	%	95% CI	*n*	%	95% CI
Grade ≥2 fibrosis boost area	58	10.4	7.8, 12.9	44	8.6	6.1, 11.0	37	8.5	5.9, 11.1	13	6.6	3.1, 10.0
Fibrosis non-boost area	269	47.9	43.7, 52.0	224	43.9	39.6, 48.2	215	49.4	44.7, 54.1	74	37.4	30.6, 44.1
Grade ≥2 telangiectasia	6	1.1	0.2, 1.9	15	2.9	1.5, 4.4	16	3.7	1.9, 5.5	7	3.5	1.0, 6.1
Edema breast	147	26.2	22.5, 29.8	69	13.5	10.5, 16.4	48	11.0	8.1, 14.0	12	6.1	2.7, 9.4
Pain chest wall	68	12.2	9.5, 14.9	36	7.0	4.8, 9.2	29	6.7	4.3, 9.0	15	7.5	3.9, 11.2
Rib fracture	1	0.2	−0.2, 0.5	4	0.8	0.02, 1.5	1	0.2	−0.2, 0.7	1	0.5	−0.5, 1.5
Cosmetic outcome fair or poor	191	34.0	30.1, 37.9	181	35.4	31.3, 39.6	172	39.7	35.1, 44.3	71	35.9	29.2, 42.5

Abbreviation: CI = confidence interval.

our series could result in a bigger therapeutic advantage compared with the sequential boost technique.

In our series, fibrosis, either in the boost or in the non-boost area, is not increased compared with the known literature. However, patients treated with chemotherapy sequentially to RT had an elevated risk of developing fibrosis in the boost area, compared with patients without chemotherapy. In patients receiving chemotherapy, RT before chemotherapy had an almost fivefold increased risk for the development of grade ≥2 fibrosis compared with chemotherapy first. This latter effect might be partly explained by the longer interval between surgery and RT. In all patients treated with chemotherapy before RT this interval exceeded 4 months (data not shown). Another explanation might be that the increased fibrosis was secondary to a radiation recall reaction after chemotherapy. We could not confirm this in our series, because unexpected skin reactions after chemotherapy were not assessed in the standard follow-up program. Furthermore, several studies, mainly using cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) showed a negative effect of chemotherapy on the development of fibrosis (11, 13, 14). However, none of these studies specifically compared chemotherapy followed by RT with RT before chemotherapy and compared mainly with concurrent chemotherapy and RT. Although the sequences of chemotherapy and RT were considered as separate covariates, Collette *et al*. (13) found that chemotherapy during RT increased the 10-year risk of fibrosis in the boost area. In our series, chemotherapy was not given concurrently with RT.

We observed an increased risk of fibrosis outside the boost area with increasing tumor size and after re-resection. This is the only

Table 3 Multivariate logistic regression models of toxicity

Dependent variable	Predictor variable	OR	95% CI	*p*
Grade ≥2 fibrosis boost at 36 mo (n = 426)	Treatment sequence			0.008
	Surgery-RT	1		
	Chemotherapy-RT	0.57	0.19, 1.69	0.31
	RT-chemotherapy	2.78	1.29, 6.00	0.009
Fibrosis non-boost at 36 mo (n = 425)	Tumor size (mm)	1.06	1.03, 1.09	<0.001
	Re-resection			
	No	1		
	Yes	2.19	1.19, 4.03	0.012
Edema breast at 12 mo (n = 535)	Axillary clearance			
	No	1		
	Yes	2.81	1.83, 4.32	<0.001
	Tumor size (mm)	1.04	1.01, 1.07	0.004
Pain chest wall at 12 mo (n = 532)	Age at start RT (y)			
	≤50	1		
	>50	0.41	0.23, 0.72	0.002
	Boost dosage			
	Low (64.4 Gy)	1		
	High (67.2 Gy)	2.06	1.16, 3.67	0.01
Fair/poor cosmetic outcome at 36 mo (n = 423)	Re-resection			
	No	1		
	Yes	4.52	2.42, 8.45	<0.001
	Tumor size (mm)	1.05	1.02, 1.08	0.001
	Regional RT			
	No	1		
	Yes	2.89	1.17, 7.14	0.02

Abbreviations: OR = odds ratio; CI = confidence interval; RT = radiotherapy.

study investigating the effect of re-resection on the development of fibrosis. No RT-associated predictors were correlated with the development of fibrosis, either in the non-boost or the boost area.

Telangiectasia grade ≥2 was observed in 48 patients (3.7%) at 3 years of follow-up. The reported incidence of telangiectasia ranges from 3.1% to 32.1% (9−11). Lilla *et al*. (9), who found telangiectasia in 32.1%, identified several factors, such as older age, higher normalized tissue dose, and acute skin toxicity, related to the presence of telangiectasia. Another factor related to telangiectasia is systemic therapy with CMF (14). We did not identify any significant prognostic factors for the development of telangiectasia.

The prevalence of breast edema and pain to the chest wall decreased over time, suggesting transient effects. Edema of the breast has been described as occurring in 2.5%−17.7% of women undergoing breast irradiation after breast-conserving surgery (9−11, 15). These results are comparable to those found in the present series.

Pain at the chest wall, specifically after BCT, has been investigated to a limited degree. We identified only one study reporting chest wall pain after breast cancer surgery (16). This study reported that 25.1% of 3253 patients complained of chest wall pain at 26 months (median) after surgery. No differences in prevalence of pain were found according to type of surgery (BCT or mastectomy) (16). In the present study, 1 year after RT, risk of pain to the chest wall was doubled in patients treated with high boost dosage, with an absolute increase from 10.2% in the low boost group to 18.9% in the high boost dosage group. This finding might reflect a dose−effect relationship of the dose to the ribs, connective tissue, and muscles.

Young age (≤50 years) only had impact on the presence of pain to the chest wall 1 year after irradiation. Younger patients had more pain complaints and used more pain medication. Similar results were previously found in a nationwide Danish survey study (17), in which younger age was associated with the development of chronic pain after breast cancer treatment. In this survey, this age-related finding was explained by the misattribution of pain and the decreased tendency to label a sensation as painful with increasing age (16). Rib fractures were observed infrequently, with seven events (0.7%). This number is consistent with other series, reporting 0.3%−2.2% rib fractures after BCT (18).

Cosmetic outcome can be considered as the end result of all breast-related toxicities and is known to impact quality of life. In our series, the physician-rated fair to poor CO was 39.7% at 3 year of follow-up. In the literature, a wide variety of scores have been reported, from 21% to 45% (10, 15, 19). The wide range of scores can be partly explained by differences in the use of evaluation instruments for CO. We used the 4-point scale from Harris (6), which is easy in routine use, with only a modest reduction of interrater reliability compared with multi-item scales (20). However, it is shown that a single evaluator instead of a panel assessment may impair reliability (20).

Numerous factors have been identified as impacting CO after BCT (10, 14, 15, 19). We identified the performance of a re-resection as the most important predictor for a fair to poor CO. Although investigated as a candidate risk factor in other studies (15, 19), only Hau *et al*. (15), in a recent analysis on panel-rated CO, reported re-resection as a predictor for poor CO. In our series, increasing pathologic tumor size was associated with poor CO. Volume differences and deformation between the two breasts are the most important factors in the physicians' assessment of global CO. These volume differences are caused by the performance of a re-resection, and larger tumors result in larger excised volumes.

The prospective data collection and the large number of patients included, combined with multiple measurements over time, are unique for this study. However, one limitation is the relatively short follow-up time, given that complications of RT can be present more than 10 years after treatment (17). Furthermore, in our study we were not able to consider large breast size, a factor that could negatively influence toxicity (10, 19).

In conclusion, the hypofractionated 3D-CRT-SIB technique as part of BCT is safe regarding normal tissue complications. Fibrosis in the boost area was not associated with RT parameters. Cosmetic outcome was influenced most by the performance of a re-resection. Furthermore, young age was found to be prognostic for the risk of pain to the chest wall.

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